matrix metalloproteinases play a significant role in cartilage destruction.
Objective: To determine if RAR-alpha is expressed in the synovial membrane (SM) of patients with OA.
Methods: SM specimens from 17 patients with OA and 14 patients with rheumatoid arthritis (RA), obtained during joint replacement, were used in this study. SM cryostat sections were stained for RAR-alpha using the ABC indirect immunoperoxidase method with anti-RAR-alpha rabbit polyclonal antibody (c-20; Santa Cruz). The specificity of anti-RAR-alpha polyclonal antibody was tested with western blotting.
Results: Immunoreactivity for RAR-alpha was detected in SM biopses from all patients with OA and RA. It was present in around 30% of mononuclear cells in nodular infiltrates, as well as in endothelial cells, synovial lining cells, and fibroblast-like cells.
Conclusion: The presence of RAR-alpha in SM of patients with OA suggests that RAR-alpha may play a role in cartilage destruction in OA.

P125

THE EFFICACY OF TOPICALLY APPLIED KETOPROFEN VERSUS CELECOXIB AND PLACEBO IN OSTEOARTHRITIS (OA) OF THE KNEE

M Rother[1], BJ Lavins[2], J Gu[2], W Kneer[3], K Lehnhardt[4], EJ Seidel[5], S Mazgareanu[1]
[1]Clinical Development, IDEA AG, Munich, Germany; [2]McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, PA; [3]Orthopedic Practice, Stockach, Germany; [4]Orthopedic Practice, Bad Duerrheim, Germany; [5]Physical & Rehabilitation Medicine, Sophien- and Hufeland Hospital, Weimar, Germany

Purpose: Transfersome® carriers are ultradeformable vesicles designed to deliver drugs non-invasively through the skin barrier to target muscles and joints without being cleared by the cutaneous microcirculation. Ketoprofen is an NSAID analgesic with potent additional local anti-inflammatory properties. This study compared the safety and efficacy of 110 mg of ketoprofen in Transfersome® Gel (IDEA-033) applied dermally twice daily (bid) with that of celecoxib (100 mg orally bid) and placebo in treating the signs and symptoms of OA of the knee.
Methods: This 6-week, multicenter, randomized, double-blind, double-dummy, parallel-group study was conducted in 397 subjects with knee OA who were experiencing at least moderate pain when not taking analgesic medication. To qualify for the study, subjects met the following flare criteria for the index knee at the baseline visit: pain with walking of at least 40 mm on the WOMAC visual analogue scale (VAS), an increase in pain with walking of at least 15 mm on the WOMAC VAS at baseline compared to screening, and a physician's global assessment of OA of grade 3 to 5 and at least a 1-grade increase from screening.
Results: 3 co-primary endpoints were defined *a priori*. In the intent-to-treat (ITT) analysis, for the WOMAC pain subscale, both IDEA-033 (p= 0.0041) and celecoxib (p= 0.0004) showed a statistically significant improvement in the least squares (LS) mean change from baseline at Week 6 vs. placebo. For the WOMAC physical function subscale, celecoxib showed a significant (p= 0.0100) improvement in the LS mean change from baseline at Week 6 vs. placebo; the improvement for IDEA-033 vs. placebo approached statistical significance (p=0.077). For Patient Global Assessment, both IDEA-033 (p= 0.0015) and celecoxib (p= 0.0145) showed a statistically significantly higher response to therapy at Week 6 for the LS mean values vs. placebo. Analysis of the primary efficacy endpoints by study week proved that both IDEA-033 and celecoxib were associated with progressive improvement over the six-week study period. The results of the per-protocol analysis were generally consistent with the ITT analysis; however, for the WOMAC physical function subscale, the improvement after 6 weeks with IDEA-033 was significantly (p= 0.0118) greater than with placebo. IDEA-033 was well tolerated. Overall, 53.6% of subjects treated with IDEA-033, 50.0% of subjects treated with celecoxib, and 48.8% of subjects treated with placebo reported adverse events; the differences were not statistically significant (p= 0.7116).
Conclusions: IDEA-033 was superior to placebo for 2 of the 3 primary efficacy measures in the ITT population and for all 3 primary efficacy measures in the per-protocol population. The study medications were generally well tolerated. The severity and nature of adverse events were generally similar among groups.

P126

EFFECTS OF AN ORALLY ADMINISTERED CATHEPSIN K INHIBITOR (SB-553484) ON THE BEAGLE DOG MEDIAL MENISCECTOMY MODEL OF OSTEOARTHRITIS

JR Connor[1], C LePage[1], AM Bendele[2], DH Maul[3], S Kumar[1]
[1]Musculoskeletal Diseases, GlaxoSmithKline, Collegeville, PA; [2]Bolder BioPATH, Inc., Boulder, CO; [3]Colorado State University, Fort Collins, CO

Aim: Cathepsin K is expressed in articular cartilage and synovial fibroblasts and has the capacity to degrade several bone and cartilage matrix components including collagen types 1, 2 and aggrecan indicating a potential role of cathepsin K in OA pathology. We have identified SB-553484 as an orally available potent inhibitor of dog cathepsin K (Ki = 200 pM) that exhibits 4-80 fold selectivity over other cathepsins such as L, S and B. This study investigated the effects of SB-553484 on chondroprotection in the dog meniscectomy model of OA.
Methods: Female beagle dogs had unilateral partial medial meniscectomy on the left knee and were treated with vehicle (n=20) or SB-553484, po, bid, at 50 mg/kg (n=20) beginning 1 day before and continuing for 4 weeks post surgery. Left knees were evaluated 4 weeks post surgery for effects of treatment on gross and microscopic histological changes. Parameters for the groups were compared using the Student's t-test with significance set at $p \leq 0.05$.
Results: All dogs tolerated the treatment and exhibited normal activity and appetite. Typical degenerative changes characterized by the presence of focal, well circumscribed lesions of cartilage degeneration were present on the medial tibias and to lesser extent on femoral condyles of all dogs in the vehicle control group. Subjective gross cartilage degeneration scores were decreased significantly by 29% in SB-553484 treated dogs. Calculated (length X width X depth) gross tibial scores were decreased significantly by 46% in SB-553484 treated dogs. Combined subjective tibial and femoral cartilage degeneration scores were decreased significantly by 28% in SB-553484 treated dogs whereas calculated summed scores were decreased non-significantly by 39%. Histopathological evaluation of the vehicle-treated dogs revealed typical degenerative changes with the most severe tibial lesions in the mid-tibia. Summed tibial cartilage degeneration decreased significantly by 21% in the SB-553484 group. Inhibition of cartilage degeneration in 4 zones from outside (1) to far inside (4) was significant for zone 1 (32%) and 16-22% for all other zones. Significant tibial cartilage degeneration width was non-significantly decreased by 21%. Overall depth ratio of any tibial matrix change was decreased significantly by 28% and the range of decrease across the 4 zones was 17-53%.
Conclusion: In summary, this study demonstrated mild to moderate beneficial effects of oral treatment with SB-553484 on gross and histopathological parameters measured in meniscectomy induced cartilage degeneration in beagle dogs. The data suggest that targeting cathepsin K may represent a valid strategy for pharmaceutical intervention in osteoarthritis.